Remarks/Arguments:

Claims 10, 17-19, 21, 30, 39, 49, 63, 83-84, and 93-96 are canceled without prejudice. Claims 1, 6, 35, 44, and 58 are amended. Support for these amendments can be found throughout the application as originally filed and are discussed in detail below. No new matter is introduced.

Claims 1-3, 5-8, 10, 12-13, 17-19, 21, 26-28, 30, 35-37, 39, 44-47, 49, 52-53, 58-61, 63, 74, and 81-96 are pending. Reexamination and reconsideration of the application, as amended, are respectfully requested.

Claim Objections

Claims 6-8, 10, 12-13, 17-19, 21, 26-28, 30, 35-37, 39, 44-47, 49, 52-53, 58-61, 63, 74, and 81-96 are objected to for the use of the acronym "LOH."

Applicant has amended the claims to recite "loss of heterozygosity" in place of "LOH."

Applicant respectfully submits that the objections have been overcome and should be withdrawn.

New Matter

Claims 26-28, 30, 35-37, 39, 44-47, 49, 52-53, 58-61, 63, 74, and 81-96 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Applicant respectfully traverses this rejection.

Claim 26 and the dependents thereof stand rejected for the recitation of "the probability for the subject to suffer form a progressing cancer is higher than the probability for the subject to suffer from a non-progressing cancer." The Office Action indicates that the specification does not provide a teaching or suggestion for the recitation.

Claim 26 has been amended and no longer recites said passage. Applicant respectfully submits that the rejection has been overcome and should be withdrawn.

Claim 44 and the dependents thereof stand rejected for the recitation of "the subject has a low probability of survival if the subject has not responded to biochemotherapy." The Office Action indicates that the specification does not provide a teaching or suggestion for the recitation.

Claim 44 has been amended and no longer recites said passage. Applicant respectfully submits that the rejection has been overcome and should be withdrawn.

Claim Rejections Under 35 USC § 112, First Paragraph

Claims 1-3, 5-8, 10, 12-13, 17-19, 21, 26-28, 30, 35-37, 39, 44-47, 49, 52-53, 58-61, 63, 74, and 81-96 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement.

Claims 10, 17-19, 21, 30, 39, 49, 63, 83-84, and 93-96 have been canceled without prejudice, thus the rejection against these claims are now moot.

Accordingly, claims 1-3, 5-8, 12-13, 26-28, 35-37, 44-47, 52-53, 58-61, 74, and 81-82, 85-92 stand rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Applicant respectfully traverses this rejection.

The Office states the following about the specification regarding enablement:

(1) does not teach that markers for 12q22-23 are markers of APAF-1 (Office Action, page 13, paragraph 2).

(2) does not teach a statistically significant relationship between 12q22-23 loss of heterozygosity and "any" cancer, but does teach said relationship with melanoma (Office Action, page 12, last paragraph), therapeutic response and

outcome, before but not after chemotherapy (Office Action, page 13, paragraphs 2-3).

(3) does teach loss of heterozygosity in DNA markers D12S1657, D12S393, D12S1706, and D12S346 in deproteinized blood is correlated with the incidence and progression of melanoma, but is not correlated with loss of heterozygosity in alleles in urine, sputum, sperm, etc for melanoma, breast, or colon cancer (Office Action, page 13, last paragraph to page 14, 1st paragraph).

(4) it would be unpredictable to determine if loss of heterozygosity in DNA markers D12S1657, D12S393, D12S1706, and D12S346 in urine, sputum, sperm, feces, etc is diagnostic or indicative of anything, since the specification only provides support for loss of heterozygosity in blood, plasma, or serum samples (Office Action, page 16, paragraph 2).

(5) it would be unpredictable to associate the outcome of treatments with any biochemotherapy or multiple rounds of biochemotherapy as the specification teaches a single round of therapy of biochemotherapy of dacarbazine, cisplatin, vinblastin, interferon, alpha-2b, IL-2, and tamoxifen (Office Action, page 18, paragraph 1).

(6) it would be unpredictable to determine survival in melanoma patients based solely on by the loss of heterozygosity in DNA markers D12S1657, D12S393, D12S1706, and D12S346, since the specification suggests that the loss of heterozygosity is predictive of only melanoma survival and not "any" survival (Office Action, page 18, paragraph 3).

Claim 1 has been amended as follows:

A method of detecting DNA markers, comprising:

providing a sample containing DNA from a human subject, wherein the DNA exists as acellular DNA in the subject; and

detecting one or more DNA markers selected from the group consisting of D12S1657, D12S393, D12S1706, and D12S346 on the DNA, wherein said acelluar DNA is from a serum sample or plasma sample.

Applicants respectfully submit that claim 1 as amended is fully enabled by because the specification provides sufficient guidance to one skilled in the art on how to detect DNA markers in acellular DNA from a serum or plasma sample (specification page 8, lines 9-12 & page 11, line 20 to page 12, line 20.

Accordingly, amended claim 1 is in compliance with the written description requirement. Likewise, dependent claims 2-3, 74, and 81 are also in compliance with the written description requirement for at least the same reasons as claim 1. Applicant respectfully submits that the rejections have been overcome and should be withdrawn.

Claim 6 has been amended as follows:

A method of detecting melanoma, comprising:

providing a sample containing DNA from a human subject, wherein the DNA exists as acellular DNA in the subject; and

analyzing DNA markers in the *12q22-23* region comprising D12S1657, D12S393, D12S1706, and D12S346 on the DNA, wherein loss of heterozygosity of any of D12S1657, D12S393, D12S1706, and D12S346 is

indicative of melanoma, and wherein said acelluar DNA is from a serum sample or plasma sample.

Applicants respectfully submit that claim 6 as amended is fully enabled by because the specification provides sufficient guidance to one skilled in the art on how to detect melanoma by analyzing DNA markers in the *12q22-23* region. As indicated above in (3) and (4), the Office Action acknowledges that the specification does teach loss of heterozygosity in DNA markers D12S1657, D12S393, D12S1706, and D12S346 in deproteinized blood is correlated with the incidence and progression of melanoma and that the loss of heterozygosity may be determined in blood, plasma, or serum samples.

Accordingly, amended claim 6 is in compliance with the written description requirement. Likewise, dependent claims 7-8, 12-13, and 82 are also in compliance with the written description requirement for at least the same reasons as claim 6. Applicant respectfully submits that the rejections have been overcome and should be withdrawn.

Claim 26 has been amended as follows:

A method of monitoring progression of melanoma comprising:

providing a melanoma tissue sample containing DNA from a human subject suffering from melanoma; and

analyzing DNA markers comprising D12S1657, D12S393, D12S1706, and D12S346 on the DNA, wherein loss of heterozygosity of any of D12S1657, D12S393, D12S1706, and D12S346 indicates the progression of melanoma in said subject.

Applicants respectfully submit that claim 26 as amended is fully enabled by because the specification provides sufficient guidance to one skilled in the art on how to monitor the progression of melanoma. As indicated above in (3), the Office Action acknowledges that the specification does teach loss of heterozygosity in DNA markers D12S1657, D12S393, D12S1706, and D12S346 in deproteinized blood is correlated with the incidence and progression of melanoma.

Accordingly, amended claim 26 is in compliance with the written description requirement. Likewise, dependent claims 27-28 and 85-86 are also in compliance with the written description requirement for at least the same reasons as claim 26. Applicant respectfully submits that the rejections have been overcome and should be withdrawn.

Claim 35 has been amended as follows:

> A method of predicting the efficacy of a melanoma biochemotherapy, comprising:
>
> providing a melanoma tissue sample containing DNA from a human subject suffering from stage IV melanoma prior to administration of a biochemotherapy; and
>
> analyzing DNA markers comprising D12S1657, D12S393, D12S1706, and D12S346 on the DNA, wherein loss of heterozygosity of any of D12S1657, D12S393, D12S1706, and D12S346 indicates poor efficacy of the biochemotherapy in the subject, and wherein said biochemotherapy comprises dacarbazine, cisplatin, vinblastin, interferon, alpha-2b, IL-2, and tamoxifen.

Applicants respectfully submit that claim 35 as amended is fully enabled by because the specification provides sufficient guidance to one skilled in the art on how to predict the efficacy of a melanoma biochemotherapy. As indicated above in (2) and (5), the Office Action acknowledges that the specification does teach a statistically significant relationship between loss of heterozygosity with melanoma and therapeutic response and outcome, wherein a single round of therapy of biochemotherapy of dacarbazine, cisplatin, vinblastin, interferon, alpha-2b, IL-2, and tamoxifen is used.

Accordingly, amended claim 35 is in compliance with the written description requirement. Likewise, dependent claims 36-37 and 87-88 are also in compliance with the written description requirement for at least the same reasons as claim 35. Applicant respectfully submits that the rejections have been overcome and should be withdrawn.

Claim 44 has been amended as follows:

> A method of determining the probability of melanoma survival, comprising:
>
> providing a melanoma tissue sample containing DNA from a human subject suffering from a stage III or IV melanoma; and
>
> analyzing DNA markers comprising D12S1657, D12S393, D12S1706, and D12S346 on the DNA, wherein loss of heterozygosity of any of D12S1657, D12S393, D12S1706, and D12S346 indicates that the subject has a low probability of surviving melanoma.

Applicants respectfully submit that claim 44 as amended is fully enabled by because the specification provides sufficient guidance to one skilled in the art on

how to determine the probability of melanoma survival. As indicated above in (6), the Office Action acknowledges that the specification does teach the loss of heterozygosity in DNA markers is predictive of melanoma survival.

Accordingly, amended claim 44 is in compliance with the written description requirement. Likewise, dependent claims 45-47, 52-53, and 89-90 are also in compliance with the written description requirement for at least the same reasons as claim 44. Applicant respectfully submits that the rejections have been overcome and should be withdrawn.

Claim 58 has been amended as follows:

> A method of determining the probability of responsiveness to a round melanoma biochemotherapy, comprising:
>
> providing a melanoma tissue sample containing DNA from a human subject suffering from stage IV melanoma prior to administration of biochemotherapy; and
>
> analyzing DNA markers comprising D12S1657, D12S393, D12S1706, and D12S346 on the DNA, wherein loss of heterozygosity of any of D12S1657, D12S393, D12S1706, and D12S346 indicates a low probability of responsiveness to the biochemotherapy in the subject, and wherein said biochemotherapy comprises dacarbazine, cisplatin, vinblastin, interferon, alpha-2b, IL-2, and tamoxifen.

Applicants respectfully submit that claim 58 as amended is fully enabled by because the specification provides sufficient guidance to one skilled in the art on

how to determine the probability of responsiveness to a round melanoma biochemotherapy. As indicated above in (2) and (5), the Office Action acknowledges that the specification does teach a statistically significant relationship between 12q22-23 loss of heterozygosity with melanoma and therapeutic response and outcome, wherein a single round of therapy of biochemotherapy of dacarbazine, cisplatin, vinblastin, interferon, alpha-2b, IL-2, and tamoxifen is use

Accordingly, amended claim 58 is in compliance with the written description requirement. Likewise, dependent claims 59-61 and 91-92 are also in compliance with the written description requirement for at least the same reasons as claim 58. Applicant respectfully submits that the rejections have been overcome and should be withdrawn.

Claim Rejections Under 35 USC § 112, Second Paragraph

Claims 17-19, 21, 83 and 84 stand rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. The Applicant respectfully traverses this rejection.

The Office states that the recitation of "probability for the subject to be suffering from a primary cancer is higher than the probability for the subject to be suffering from a primary cancer" is unclear.

The claims been amended and no longer recites said passage. Applicant respectfully submits that the rejection has been overcome and should be withdrawn.

Claim Rejections Under 35 USC § 102

Claims 1, 5, 6, 10, 12, 13, and 17 stand rejected under 35 U.S.C. 102(b) as being anticipated by Soengas, et al. (Nature 409:207-211).

Claims 5, 17, and 17 have been canceled without prejudice, thus the rejection against these claims are now moot.

Accordingly, claims 1, 6, 12, and 13 stand rejected under 35 U.S.C. § 102, as being anticipated by Soengas. Applicant respectfully traverses this rejection.

Claim 1 has been amended as follows:

> A method of detecting DNA markers, comprising:
>
> providing a sample containing DNA from a human subject, wherein the DNA exists as acellular DNA in the subject; and
>
> detecting one or more DNA markers selected from the group consisting of D12S1657, D12S393, D12S1706, and D12S346 on the DNA, wherein said acelluar DNA is from a serum sample or plasma sample.

Applicant respectfully submits that Soengas fails to disclose or teach a method of detecting DNA markers in acellular DNA from serum or plasma, as required by claim 1. In contrast, Soengas discloses a method of detecting markers using frozen tumor specimen. Therefore, Soengas does not teach or suggest the detection method of claim 1.

The Office Action indicates that the term "acellular" is not specifically defined by the specification. Applicant respectfully submits that the specification discloses that acellular may be a serum sample or plasma sample. See page 3, line 11 and page 10, lines 21-23. In light of the foregoing, Applicant respectfully submits that Soengas does not anticipate claim 1, because the cited reference fails to teach or suggest to use serum or plasma samples.

Claim 6 has been amended as follows:

> A method of detecting melanoma, comprising:

providing a sample containing DNA from a human subject, wherein the DNA exists as acellular DNA in the subject; and

analyzing DNA markers in the *12q22-23* region comprising D12S1657, D12S393, D12S1706, and D12S346 on the DNA, wherein loss of heterozygosity of any of D12S1657, D12S393, D12S1706, and D12S346 is indicative of melanoma, and wherein said acelluar DNA is from a serum sample or plasma sample.

As indicated above Soengas fails to disclose or teach a method of detecting melanoma using acellular DNA from serum or plasma, as required by claim 6.

Accordingly, Soengas does not anticipate the present claims 1 and 6. Likewise, dependent claims 12-13 are also patentable over Soengas for at least the same reasons as claims 1 and 6. In view of the foregoing, Applicant respectfully requests that the Office withdraw the rejection.

Claim Rejections Under 35 USC § 103

Claims 35, 39-40, and 58-59 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Soengas, et al. (Nature, 2001, 409:207-211).

Claims 39-40 has been canceled without prejudice, thus the rejection against this claim is now moot.

Accordingly, claims 35 and 58-59 stand rejected under 35 U.S.C. 103(a) as being unpatentable. Applicants respectfully traverse this rejection.
Claim 35 has been amended as follows:

A method of predicting the efficacy of a melanoma biochemotherapy, comprising:

providing a melanoma tissue sample containing DNA from a human subject suffering from stage IV melanoma prior to administration of a biochemotherapy; and

analyzing DNA markers comprising D12S1657, D12S393, D12S1706, and D12S346 on the DNA, wherein loss of heterozygosity of any of D12S1657, D12S393, D12S1706, and D12S346 indicates poor efficacy of the biochemotherapy in the subject, and wherein said biochemotherapy comprises dacarbazine, cisplatin, vinblastin, interferon, alpha-2b, IL-2, and tamoxifen.

Claim 58 has been amended as follows:

A method of determining the probability of responsiveness to a round melanoma biochemotherapy, comprising:

providing a melanoma tissue sample containing DNA from a human subject suffering from stage IV melanoma prior to administration of biochemotherapy; and

analyzing DNA markers comprising D12S1657, D12S393, D12S1706, and D12S346 on the DNA, wherein loss of heterozygosity of any of D12S1657, D12S393, D12S1706, and D12S346 indicates a low probability of responsiveness to the biochemotherapy in the subject, and wherein said biochemotherapy comprises dacarbazine, cisplatin, vinblastin, interferon, alpha-2b, IL-2, and

tamoxifen.

Applicant respectfully submits that Soengas fails to disclose or teach a method of predicting the efficacy of a melanoma biochemotherapy or a method of determining the probability of responsiveness to a round melanoma biochemotherapy, as required by claims 35 and 58. In contrast, Soengas discloses a method of detecting the loss of Apaf-1 expression in various tumor types including metastatic melanoma, but does not teach or disclose using stage IV melanoma tissue samples or biochmeotherapy comprising dacarbazine, cisplatin, vinblastin, interferon, alpha-2b, IL-2, or tamoxifen.

The Office Action states that Soengas teaches LOH analysis from tumor samples, but does not teach that loss of heterozygosity of D12S1657, D12S393, D12S1706, and D12S346 is predictive of response to biochemotherapy or predicted efficacy of response to biochemotherapy. The Office Action further states that it would be obvious to use Soengas in the methods of claims 35 and 58 since Soengas teaches the assessment of Apaf-1 status may improve the therapeutic management of patients with malignant melanoma. Applicants respectfully submit that Soengas analyzed a series of metastatic melanoma samples (see Soengas' Supplementary Information). The metastatic melanoma samples tested include lung, gallbladder, lymph node, soft tissue, spleen, stomach, liver, and paotid tissue, but not stage IV melanoma sample. Likewise, Soengas used 5-aza-2'-deoxycytidine (5aza2dC) to treat various melanoma cell lines (abstract), but does not teach to use any of the biochemotherapy drugs as required by claims 35 and 58. In light of the foregoing, Applicant respectfully submits that Soengas does not render claims 35 and 58 obvious, because the cited reference fails to teach or suggest element of the claimed invention.

Likewise, dependent claim 59 is also patentable over Soengas for at least the same reasons as claims 35 and 58. In view of the foregoing, Applicant respectfully requests that the Office withdraw the rejection.

Claims 1-3, 5, 6-8, 10-13, 35-37, 39, 58, 59-61, 63, 74, and 81-92 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Soengas, et al. (Nature, 2001, 409:207-211) in view of Gocke et al. (U.S. Pat. No. 6,156,504).

Claims 5, 10, 39, 63, and 83-84 have been canceled without prejudice, thus the rejection against these claims are now moot.

Accordingly, claims 1-3, 6-8, 11-13, 35-37, 58, 59-61, 74, 81- 82, and 85-92 stand rejected under 35 U.S.C. 103(a) as being unpatentable. Applicants respectfully traverse this rejection.

As discussed above, Applicants respectfully submit that Soengas fails to teach or disclose the following: (a) method of detecting DNA markers in acellular DNA from serum or plasma, as required by claim 1; (b) a method of detecting melanoma using acellular DNA from serum or plasma, as required by claim 6; (c) method of predicting the efficacy of a melanoma biochemotherapy; and (d) a method of determining the probability of responsiveness to a round melanoma.

Gocke is not seen to remedy the defects of Soengas and the Office does not rely upon the reference for such. Instead, Gocke is cited for its relevance regarding the use of serum or plasma for DNA amplification. As such, the combined teachings of the prior art fail to teach or suggest each element of the claimed invention. As such, the combination suggested by the Office cannot render the claimed invention obvious.

Accordingly, Soengas in view of Gocke is not obvious over independent claims 1, 6, 35, 58, and 85. Likewise, dependent claims 2-3, 7-8, 11-13, 36-37, 59-61, 74, 81- 82, and 85-92 are also patentable over Soengas in view of Gocke for at least the same reasons as the independent claims. In view of the foregoing, Applicant respectfully requests that the Office withdraw the rejection.

Double Patenting

Claims 1, 6, 17, and 26 stand provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1, 7, 9, 11, 17, and 23 of co-pending U.S. Patent Application No. 10/809,956 (Applicants believe that the Examiner meant U.S. Patent Application No. 10/809,965). If the pending claims in either application are found to be otherwise allowable except for this ground of rejection, Applicants will submit an appropriate terminal disclaimer. In this event, Applicants request that the Examiner telephone the undersigned who will then provide the terminal disclaimer.

CONCLUSION

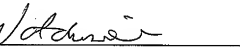
In view of the foregoing, it is respectfully submitted that the application is in condition for allowance. Reexamination and reconsideration of the application, as amended, are requested.

If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is requested to call the undersigned at the Los Angeles, California telephone number (310)785-4617 to discuss the steps necessary for placing the application in condition for allowance.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-1314.

Respectfully submitted,
HOGAN & HARTSON L.L.P.

Dated: June 6, 2008

By: 

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